(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 987 274 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
22.03.2000 Bulletin 2000/12

(51) Int. Cl.[7]: **C07K 5/11**, C07K 5/09, A61K 38/06, A61K 38/07

(21) Application number: **98117506.0**

(22) Date of filing: **15.09.1998**

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
AL LT LV MK RO SI

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(54) Factor VIIa Inhibitors

(57) The present invention relates to novel compounds, their preparation, their use and pharmaceutical compositions containing the compounds which have a strong antithrombotic effect through reversible inhibition of activated blood coagulation factor VIIa (FVIIa).

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Printed by Xerox (UK) Business Services
2.16.7/3.6

system, additional factor Xa is produced via the thrombin-mediated activity of the intrinsic pathway. Thus, thrombin plays a dual autocatalytic role, mediating its own production and the conversion of fibrinogen to fibrin.

[0005] The autocatalytic nature of thrombin generation is an important safeguard against uncontrolled bleeding and it ensures that, once a given threshold level of prothrombinase is present, blood coagulation will proceed to completion. The ability to form blood clots is vital to survival. In certain disease states, however, the formation of blood clots within the circulatory system is itself a source of morbidity. It is nevertheless not desirable in such disease states to completely inhibit the clotting system because life threatening hemorrhage would ensue. Thus, it is most desirable to develop agents that inhibit coagulation by inhibition of factor VIIa without directly inhibiting thrombin.

[0006] In many clinical applications there is a great need for the prevention of intravascular blood clots or for some anti-coagulant treatment. The currently available drugs are not satisfactory in many specific clinical applications. For example, nearly 50 % of patients who have undergone a total hip replacement develop deep vein thrombosis (DVT). The currently approved therapies are fixed dose low molecular weight heparin (LMWH) and variable dose heparin. Even with these drug regimes 10 % to 20 % of patients develop DVT and 5 % to 10 % develop bleeding complications.

[0007] Another clinical situation for which better anticoagulants are needed concerns subjects undergoing transluminal coronary angioplasty and subjects at risk for myocardial infarction or suffering from crescendo angina. The present, conventionally accepted therapy, which consists of administering heparin and aspirin, is associated with a 6 % to 8 % abrupt vessel closure rate within 24 hours of the procedure. The rate of bleeding complications requiring transfusion therapy due to the use of heparin also is approximately 7 %. Moreover, even though delayed closures are significant, administration of heparin after termination of the procedures is of little value and can be detrimental.

[0008] The most widely used blood-clotting inhibitors are heparin and the related sulfated polysaccharides, LMWH and heparin sulfate. These molecules exert their anti-clotting effects by promoting the binding of a natural regulator of the clotting process, anti-thrombin III, to thrombin and to factor Xa. The inhibitory activity of heparin primarily is directed toward thrombin, which is inactivated approximately 100 times faster than factor Xa. Hirudin and hirulog are two additional thrombin-specific anticoagulants presently in clinical trials. However, these anticoagulants, which inhibit thrombin, also are associated with bleeding complications. Preclinical studies in baboons and dogs have shown that targeting enzymes involved at earlier stages of the coagulation cascade, such as factor Xa or factor VIIa, prevents clot formation without producing the bleeding side effects observed with direct thrombin inhibitors (T. Yokoyama, A.B Kelly, U.M Marzec, Hanson SR, S Kunitada, L.A Harker, Circulation 92 (1995),485-491; L.A Harker, S.R Hanson, A.B Kelly, Thromb Hemostas 74 (1995) 464-472; C.R Benedict, J Ryan, J Todd, K Kuwabara, P Tyburg, Jr. J Cartwright, D. Stern, Blood 81 (1993, 2059-2066).

[0009] Specific inhibition of the factor VIIa/TF catalytic complex using monoclonal antibody (International Application No. WO9206711) and a protein such as chloromethyl ketone inactivated FVIIa (International Appl. No. WO9612800 and WO9747651) is an extremely effective means of controlling thrombus formation caused by acute arterial injury or the thrombotic complications related to bacterial septicemia. There is also experimental evidence suggesting that inhibition of factor VIIa/TF activity inhibits restenosis following ballon angioplasty (L.A Harker, S.R Hanson, J.N Wilcox, A.B Kelly, Haemostasis 26 (1996) S1:76-82). Bleeding studies have been conducted in baboons and indicate that inhibition of the factor VIIa/TF complex has the widest safety window with respect to therapeutic effectiveness and bleeding risk of any anticoagulant approach tested including thrombin, platelet and factor Xa inhibition (L.A Harker, S.R Hanson, A.B Kelly, Thromb Hemostas 74 (1995) 464-472).

[0010] A specific inhibitor of factor VIIa would have substantial practical value in the practice of medicine. In particular, a factor VIIa inhibitor would be effective under circumstances where the present drugs of choice, heparin and related sulfated polysaccharides, are ineffective or only marginally effective. Thus, there exists a need for a low molecular weight, factor VIIa-specific blood clotting inhibitor that is effective, but does not cause unwanted side effects. The present invention satisfies this need by providing factor VIIa activity inhibiting derivatives of formula I and by providing related advantages as well.

[0011] The compounds of formula I are inhibitors of the blood clotting enzyme factor VIIa. The invention also relates to processes for the preparation of the compounds of formula I, to methods of inhibiting factor VIIa activity and of inhibiting blood clotting, to the use of the compounds of formula I in the treatment and prophylaxis of diseases which can be cured or prevented by the inhibition of factor VIIa activity such as thromboembolic diseases, and restenosis and the use of the compounds of formula I in the preparation of medicaments to be applied in such diseases. The invention further relates to compositions containing a compound of formula I in a mixture or otherwise in association with an inert carrier, in particular pharmaceutical compositions containing a compound of formula I together with pharmaceutically acceptable carrier substances and auxiliary substances.

Summary of the invention

[0012] The present invention provides compounds that specifically inhibit factor VIIa activity. The compounds of the invention have the formula I

n is an integer of from 0 to 3,

E1 is NR70, wherein R70 is selected from the group consisting of hydrogen, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl and heterocycloalkylalkyl,

E2 is CR71R72, wherein R71 and R72 are independently selected from the group consisting of hydrogen and unsubstituted or substituted alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl and heterocycloalkylalkyl,

E3 is C(O),

R2 is selected from the group consisting of NR21R22, OR23 and R24, wherein R21, R22, R23 and R24 are independently selected from the group consisting of hydrogen and unsubstituted or substituted alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl and heterocycloalkylalkyl,

and pharmaceutically acceptable salts thereof.

[0013] Preferred are compounds of the formula I
wherein

R1 is R12 CO, wherein R12 is as defined
A is A1-A2-A3, wherein

A1 is -NH-,
A2 is -CR92R93-, wherein R92 is hydrogen and R93 is as defined
A3 is -CO-,

B is B1-B2-B3, wherein

B1 is -NH-,
B2 is -CR96R97-, wherein R96 is hydrogen and R97 is as defined,
B3 is -CO-,

D is D1-D2-D3, wherein

D1 is-NH-,
D2 is -CR81R82-, wherein R81 is hydrogen and R82 is as defined,
D3 is -CO-,

E_n is $(E1\text{-}E2\text{-}E3)_n$, wherein

n is 1 or 2,
E1 is -NH-,
E2 is -CR71R72-, wherein R71 is hydrogen and R72 is as defined,
E3 is -CO-, and

R2 is as defined.

[0014] Particularly preferred are the above indicated preferred compounds of the formula (I) wherein n is 1 and R2 is NHR22, wherein R22 is as defined.

[0015] Specific examples of the compounds of the invention include, for example, the compounds listed in Table 2 below.

[0016] The compounds of the formula I can be prepared by

a1) attaching a compound of the formula Fmoc-E_n-OH or Fmoc-D1-D2-COOH, where Fmoc is 9-fluorenylmethoxycarbonyl and E_n, D1 and D2 are as hereinbefore defined, to a Rink-amide resin and then cleaving off the protecting group Fmoc,
a2) repeating the procedure as described in step a1) above with Fmoc-B1-B2-COOH,

Table 1

Abbreviations used in the specification

Compound	Abbreviation No. 1	Abbreviation No. 2*
Alanine	Ala	A
Allyloxycarbonyl	Alloc	
m-Amidinophenylalanine	m-Aph	
p-Amidinophenylalanine	p-Aph	
2-Aminobutyric acid	2-Abu	
Arginine	Arg	R
Asparagine	Asn	N
Aspartic acid	Asp	D
Benzoyl	Bz	
Benzyl	Bzl	
t-Butyloxycarbonyl	Boc	
t-Butyl	tBu	
γ-Carboxyglutamic acid	Gla	
Cyclohexyl	Chx	
Cyclohexylalanine	Cha	
Cysteine	Cys	C
2,4-Diaminobutyric acid	Dab	
2,3-Diaminopropionic acid	Dap	
Dichloromethane	DCM	
Diisopropylcarbodiimide	DIC	
Diisopropyethylamine	DIEA	
N,N-Dimethylformamide	DMF	
Dimethylsulfoxide	DMSO	
9-Fluorenylmethyloxycarbonyl	Fmoc	
Glutamic acid	Glu	E

teases, including plasmin and thrombin (using the same concentration of the inhibitor). Such proteases are involved in the blood coagulation and fibrinolysis cascade.

[0021] As used herein, the term "substituent" refers to any of various chemical groups that is substituted onto the peptide backbone or side chain of a peptide, peptide analogue, mimetic or organic compound disclosed herein. A substituent can include any of a variety of different moieties known to those skilled in the art (see, for example, Giannis and Kolter, Angew. Chem. Int. Ed. Engl. 32:1244-1267 (1993), which is incorporated herein by reference).

[0022] As used herein, the term "alkyl" is used in the broadest sense to mean saturated or unsaturated, linear, branched or cyclic chains of about 1 to 13 carbon atoms. Thus, the term "alkyl" includes, for example, methyl, ethyl, n-propyl, isopropyl, sec-butyl, 1 -methylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 2,2-dimethylpropyl, n-pentyl and n-hexyl groups, alkylene groups, cyclic chains of carbon atoms such cyclohexyl and cyclopentyl groups, as well as combinations of linear or branched chains and cyclic chains of carbon atoms such as a methyl-cyclohexyl or cyclopropyl-methylene group. In addition, it should be recognized that an alkyl as defined herein can be substituted with a substituent. Similarly, the term "acyl" is used in its broadest sense to mean saturated or unsaturated, linear, branched or cyclic chains of about 1 to 13 carbon atoms or aryl groups having 5 to 13 carbon atoms, which contain a carboxyl group. Thus, the term "acyl" encompasses, for example, groups such as formyl, acetyl, benzoyl and the like.

[0023] Preferably, the term „alkyl" means saturated, linear or branched chains of from 1 to 6 carbon atoms, unsaturated linear or branched chains of from 2 to 6 carbon atoms, or cyclic alkyl groups of from 3 to 6 carbon atoms, preferred of from 4 to 6 carbon atoms. From the unsaturated alkyl chains, C_2-C_6-alkenyl and C_2-C_6-alkynyl are preferred.

[0024] Preferably, the term „acyl" means the hereinbefore mentioned saturated or unsaturated, linear, branched or cyclic chains having the preferred range of carbon atoms, which contain a carboxyl group.

[0025] The term "aryl" refers to aromatic groups containing about 5 to 13 carbon atoms and at least one "ring" group having a conjugated pi electron system. Preferable, the term „aryl" refers to aromatic groups having 6 to 10 carbon atoms. Examples of aryls include, for example, phenyl, naphthyl, fluorenyl, biphenylyl groups, and analogues and derivatives thereof, all of which optionally can be substituted with one or more substituents. The term "arylalkyl" refers to an alkyl as defined above substituted with one or more, for example two, aryl groups. Suitable arylalkyl groups include benzyl, phenethyl, diphenylmethyl, diphenylethyl, diphenylpropyl, naphthylmethyl, naphtylethyl and the like, all of which optionally can be substituted.

[0026] The terms "heteroalkyl," "heteroarylalkyl" and "heteroaryl" also are used herein and refer to an alkyl, an arylalkyl and an aryl, respectively, wherein one or more carbon atoms are replaced with one or more heteroatoms such as a N, O or S atom. In addition, the term "heterocycloalkyl" is used in reference to a cyclic alkyl group that is substituted with one or more heteroatoms. Preferably, the term „heterocycloalkyl" means a cycloalkyl group having 3 to 8 carbon atoms, of which 1 to 3 are replaced with hetero atoms such a N, O or S atoms. Suitable heteroaryl groups, heteroarylalkyl groups and heteroalkyl groups include, for example, pyridyl, thienyl, indolyl, imidazolyl, furyl, piperonyl, picolyl, pyrrolidinyl, piperidyl, tetrahydrofuryl, morpholinyl, piperazinyl and the like, all of which can optionally be substituted.

[0027] The peptides of the invention can be modified at the N-terminus and/or the C-terminus by reaction with suitable reagents or by introduction (or by the presence of) an amino-protecting group or carboxy-protecting group, respectively. The N-terminus of a peptide or peptide analog can be chemically modified such that the N-terminus amino group is substituted, for example, by an acyl group (for example acetyl, cyclopentylcarboxy, isoquinolylcarboxy, furoyl, tosyl, benzoyl, pyrazinecarboxy or other such group), by reaction with an isocyanate, chloroformate, alkylating agent or by introducing other such group, all of which can be substituted by a substituent as described above. It should be recognized that the term "amino group" is used broadly herein to refer to any free amino group, including a primary, secondary or tertiary amino group, present in a peptide. In comparison, the term "N-terminus" refers to the α-amino group of the first amino acid present in a peptide written in the conventional manner.

[0028] The N-terminus of a peptide of the invention can be protected by linking thereto an amino-protecting group. The term "amino-protecting group" is used broadly herein to refer to a chemical group that can react with a free amino group, including, for example, the α-amino group present at the N-terminus of a peptide of the invention. By virtue of reacting therewith, an amino-protecting group protects the otherwise reactive amino group against undesirable reactions as can occur, for example, during a synthetic procedure or due to exopeptidase activity on a final compound. Modification of an amino group also can provide additional advantages, including, for example, increasing the solubility or the activity of the compound. Various amino-protecting groups are disclosed herein or otherwise known in the art and include, for example, acyl groups such as an acetyl, tert-butyloxycarbonyl, allyloxycarbonyl, benzyloxycarbonyl group, benzoyl groups, as well as an aminoacyl residue, which itself can be modified by an amino-protecting group. Other amino-protecting groups are described, for example, in The Peptides, eds. Gross and Meienhofer, Vol. 3 (Academic Press, Inc., N.Y. 1981); and by Greene and Wuts, in Protective Groups in Organic Synthesis 2d ed., pages 309-405 (John Wiley & Sons, New York (1991), each of which is incorporated herein by reference. The product of any such modification of the N-terminus amino group of a peptide or peptide analog of the invention is referred to herein as an "N-terminal derivative."

[0029] Similarly, a carboxy group such as the carboxy group present at the C-terminus of a peptide can be chemically

Table 2

Factor VIIa inhibitory activities of selected compounds of the formula I	
	Ki (μM)
Alloc-pAph-Glu-Arg-Cha-NH_2	0.046
Allylaminocarbonyl-pAph-Glu-Arg-Cha-NH_2	0.042
Alloc-pAph-Glu-Arg-Chg-NH_2	0.238
Alloc-pAph-Glu-Dap[-C(=NH)-NH_2]-Cha-NH_2	0.012
Alloc-pAph-Glu-Ala[3-C(=NH)-NH_2]-Cha-NH_2	0.03
Alloc-pAph-Glu-Asn-Cha-NH_2	0.021
Alloc-pAph-Glu-Dab-Cha-NH_2	0.055
Alloc-pAph-Glu-Dap[-C(=NH)-NH_2]-NH_2	0.26
Alloc-pAph-Glu-Gly-Cha-NH_2	0.12
Alloc-pAph-Glu-Thr(Bzl)-NH-$(CH_2)_2$-$CH(Ph)_2$	0.17
Alloc-pAph-Glu-Dab-NH-CH_2-CH_2-phenyl	0.38
Alloc-pAph-Glu-Asn-NH-CH_2-Chx	0.15
Alloc-pAph-Glu-2-Abu[4-C(=NH)-CH_3]-Cha-NH_2	0.19
Alloc-pAph-Glu-Dap[-C(=NH)-CH_3]-Cha-NH_2	0.11
Alloc-pAph-Glu-Dab[-C(=NH)-NH_2]-Cha-NH_2	0.012
Alloc-pAph-Glu-2-Abu[4-CN]-Cha-NH_2	0.063
Alloc-pAph-Glu-Ala[3-CN]-Cha-NH_2	0.12
Alloc-pAph-Glu-Asn-(1-naphthyl)-methylamide	0.031
Alloc-pAph-Glu-Asn-(1-naphthyl)-1-ethylamide	0.021
Alloc-pAph-Glu-Asn-(2-naphthyl)-methylamide	0.027
Alloc-pAph-Glu-Asn-(3,4-dichlorobenzyl)-amide	0.026
Alloc-pAph-Glu-Asn-2-(3-chlorophenyl)-ethylamide	0.023
Alloc-pAph-Glu-Arg[NO_2]-Cha-NH_2	0.014
Alloc-pAph-Glu-Cys[Bzl]-Cha-NH_2	0.026
Alloc-pAph-Glu-Trp-Cha-NH_2	0.017
Alloc-pAph-Glu-Phg-Cha-NH_2	0.017
Alloc-pAph-Glu-Asn-(9-fluorenyl)-amide, or	0.023
Alloc-pAph-Glu-Asn-(3,5-ditrifluormethylbenzyl)-amide	0.033

[0038] The thrombin-inhibitory activities of the above compounds can be expressed in Ki-values which are between 500 and 1000 times as high as the above indicated factor VIIa inhibitory activities. Also, the factor Xa inhibitory activities of the above compounds as determined can be expressed in Ki-values which are at least 100 times as high as the above indicated factor VIIa inhibitory activities.

[0039] These results demonstrate that the compounds of the formula I are useful as inhibitors of factor VIIa, but do not substantially inhibit the activity of factor Xa or serine proteases such as thrombine, which are involved in the process of blood coagulation and fibrinolysis.

[0040] A compound of the invention can be used advantageously as an anticoagulant, which can be contacted with a blood sample to prevent coagulation. For example, an effective amount of a compound of the invention can be contacted with a freshly drawn blood sample to prevent coagulation of the blood sample. As used herein, the term "effective

[0048] Pharmaceutically acceptable modifications also can include, for example, the formation of peptide amides. Such amide modifications, which can be effected upon the compounds of the invention, include, for example, those derived from ammonia, primary C_1 to C_6 dialkyl amines, where the alkyl groups are straight or branched chain, or arylamines having various substitutions. In the case of secondary amines, the amine also can be in the form of a 5 or 6 membered heterocycle containing, for example, a nitrogen atom. Methods for preparing such amides are well known in the art.

[0049] In another embodiment of the invention, a compound of the invention can be used in an assay to identify the presence of factor VIIa or to isolate factor VIIa in a substantially purified form. Preferably, the compound of the invention is labeled with, for example, a radioisotope, and the labeled compound is detected using a routine method useful for detecting the particular label. In addition, a compound of the invention can be used advantageously as a probe to detect the location or amount of factor VIIa activity in vivo, in vitro or ex vivo.

[0050] It is understood that modifications that do not substantially affect the activity of the various embodiments of this invention are included within the invention disclosed herein. Accordingly, the following examples are intended to illustrate but not limit the present invention.

Example 1

Peptide synthesis procedures and general synthesis procedures

[0051] Starting materials used in the synthesis were obtained from chemical vendors such as Aldrich, Sigma, Fluka, Nova Biochem and Advanced Chemtech. During the synthesis, the functional groups of the amino acid derivatives used were protected by blocking groups to prevent side reaction during the coupling steps. Examples of suitable protecting groups and their use are described in The Peptides, supra, 1981, and in Vol. 9, Udenfriend and Meienhofer ed. 1987, which is incorporated herein by reference.

[0052] General solid-phase peptide synthesis was used to produce the compounds of the invention. Such methods are described, for example, by Steward and Young (Solid Phase Peptide Synthesis (Freeman & Co., San Francisco, 1969), which is incorporated herein by reference).

[0053] Unless indicated otherwise, peptides were synthesized on TentaGel S NH_2 Resin (Rapp Polymere, Tübingen, Germany). An acid sensitive linker p-[(R,S)-α-[1-(9H-Fluoren-9-yl)-methoxyformamido]-2,4-dimethoxybenzyl]-phenoxy-acetic acid (Knorr Linker) was coupled to the solid support (Bernartowicz, et. al, Tetr. Lett. 30:4645 (1989); incorporated herein by reference). Alternatively, peptides were synthesized on polystyrene resin cross-linked with 1 % divinylbenzene modified with an acid sensitive linker (Rink resin) (Rink, Tetr. Lett. 28, 3787 (1987); Sieber, Tetr. Lett. 28, 2107 (1987), each of which is incoporated herein by reference). When peptides were synthesized by first coupling the sidechain carboxylic acid of a compound of the formula Fmoc-B1-CH(R97)-COOPG to the resin, TentaGel S NH_2 resin modified by attachment of the HMPA linker was employed. Coupling was performed using N,N'-diisopropylcarbodiimide (DIC) in the presence of an equivalent amount of HOBt, with the exception of Alloc-pAph-OH, where 2 equivalents of HOBt were used. All couplings were done in either N,N-dimethylformamide (DMF) or DMF:DMSO (1:1 mixture) at room temperature (RT). Completion of coupling was monitored by ninhydrin test. A second (double) coupling was performed where coupling in the first instance was incomplete.

[0054] Deprotection of the Fmoc group was accomplished using 50% piperidine in DMF for 2+10 min. The amount of Fmoc released was determined from the absorbance at 300 nm of the solution after deprotection, volume of washes and weight of the resin used in the synthesis.

[0055] The cycle of each coupling was as follows:

Step	Action/Reagent	Solvent
1.	0.5 g of functionalized Peptide Resin	
2.	3 fold-excess amino acid derivative/HOBt/DIC	4ml DMF
3.	Couple (min. 1h)	
4.	Wash (3 x 5 ml)	DMF
5.	Ninhydrin test	
6.	Deprotection (2+10 min)	
	Piperidine/DMF	5ml 50%

dine.

Alloc-pAph-OH

[0064] All of the Alloc-Phe(4-C(=NH)-SCH_3)-OH · HI above was dissolved in 50 ml methanol with 300 µl of acetic acid and 0.5 g of ammonium acetate was added. Mixture was heated for 3 hours to 55°C, evaporated and 10 ml of acetone was added. After 2 hours at 0°C, the solid product was filtered, washed with little cold acetone, little cold methanol and diethyl ether and dried in vacuum. Yellowish solid, yield 0.53g.

Example 3

Synthesis of Alloc-pAph-Glu-Arg-Cha-NH_2

[0065] To 1g of TentaGel S NH_2 resin (substitution 0.26mmol/g), Knorr amide linker was attached. According to general procedures outlined in Example 1, following protected amino acids were coupled: Fmoc-Cha-OH, Fmoc-Arg(Pmc)-OH, Fmoc-Glu(OtBu)-OH and Alloc-pAph. The peptide was cleaved and deprotected by mixture TFA/thioanisole (95/5) for 3 hours and processed as described in Example 1. The crude compound was purified using HPLC as described in Example 1 and characterized by MS. (M+H)+: found 729.1, calc. 729.4.

Example 4

Synthesis of Allyl-NH-CO-pAoh-Glu-Arg-Cha-NH_2

[0066] To 0.5g of TentaGel S NH_2 resin (substitution 0.26mmol/g), Knorr amide linker was attached. According to general procedures in Example 1, following protected amino acids were coupled: Fmoc-Cha-OH, Fmoc-Arg(Pmc)-OH, Fmoc-Glu(OtBu)-OH and Fmoc-Phe(4-CN). After N-terminal Fmoc deprotection, the resin was treated with solution of 1 mmol of allylisocyanate in 3 ml of DMF for 2 hours. The resin was then washed with DMF and triethylamine/pyridine(1:2) and treated with saturated solution of H_2S in pyridine/triethylamine overnight. The resin was washed with acetone and the thioamide resin was reacted with methyliodide (3 ml of 10% solution of methyliodide in acetone) for 6 hours. The methylthioimidate resin was washed with acetone, methanol and treated with solution of 0.2g ammonium acetate, 100 µl acetic acid in 3 ml of methanol at 55°C for 3 hours. The resin was washed with methanol, DMF and DCM and the peptide was cleaved and deprotected by mixture TFA/thioanisole (95/5) for 3 hours and processed as described in Example 1. The crude material was purified using HPLC as described in Example 1 and characterized by MS. (M+H)+: found 728.3, calc. 728.4.

Example 5

Synthesis of Alloc-pAph-Glu-Arg-Chg-NH_2

[0067] To 1g of TentaGel S NH_2 resin (substitution 0.26mmol/g), Knorr amide linker was attached. According to general procedures in Example 1, following protected amino acids were coupled: Fmoc-Chg-OH, Fmoc-Arg(Pmc)-OH, Fmoc-Glu(OtBu)-OH and Alloc-pAph. The peptide was cleaved and deprotected by mixture TFA/thioanisole (95/5) for 3 hours and processed as described in Example 1. The crude compound was purified using HPLC as described in Example 1 and characterized by MS. (M+H)+: found 715.8, calc. 715.4.

Example 6

Synthesis of Alloc-(D)pAph-Glu-Arg-Cha-NH_2

[0068] To 1g of TentaGel S NH_2 resin (substitution 0.26mmol/g), Knorr amide linker was attached. According to general procedures in Example 1, following protected amino acids were coupled: Fmoc-Cha-OH, Fmoc-Arg(Pmc)-OH, Fmoc-Glu(OtBu)-OH and Alloc-(D)pAph-OH (synthesized according to the same procedure as Alloc-pAph-OH in Example 2). The peptide was cleaved and deprotected by mixture TFA/thioanisole (95/5) for 3 hours and processed as described in Example 1. The crude compound was purified using HPLC as described in Example 1 and characterized by MS. (M+H)+: found 729.2, calc. 729.4.

Example 12

Synthesis of Alloc-pAph-Glu-Dab-Cha-NH_2

[0074] To 0.25g of TentaGel S NH_2 resin (substitution 0.26mmol/g), Knorr amide linker was attached. According to general procedures in Example 1, following protected amino acids were coupled: Fmoc-Cha-OH, Fmoc-Dab(Boc)-OH, Fmoc-Glu(OtBu)-OH and Alloc-pAph. The peptide was cleaved and deprotected by mixture TFA/thioanisole (95/5) for 1 hour and processed as described in Example 1. The crude compound was purified using HPLC as described in Example 1 and characterized by MS. (M+H)+: found 673.2, calc. 673.4.

Example 13

Synthesis of Alloc-pAph-Glu-Ala(3-C(=NH)-NH_2)-NH_2

[0075] To 0.25g of TentaGel S NH_2 resin (substitution 0.26mmol/g), Knorr amide linker was attached. According to general procedures in Example 1, following protected amino acids were coupled: Fmoc-Ala(3-CN)-OH, Fmoc-Glu(OtBu)-OH and Alloc-Phe(4-CN)-OH. Mixture of pyridine/triethylamine (2:1) was saturated with H_2S (RT, 15-30min) and this solution added to the resin prewashed with pyridine/triethylamine (2:1). After overnight standing, resin is washed with acetone and treated with solution of 20%methyliodide in acetone overnight. Resin was then washed with acetone and methanol. The resin bound methylthioimidate is then converted to amidine by 3 hour heating (waterbath, 55°C) of the resin with solution of 10 eq of ammonium acetate in methanol containing 5% acetic acid. After this final conversion, the resin was washed with methanol, DMF, DCM. The peptide was cleaved and deprotected by mixture TFA/thioanisole (95/5) for 1 hour and processed as described in Example 1. The crude compound was purified using HPLC as described in Example 1 and characterized by MS. (M+H)+: found 533.3, calc. 533.2.

Example 14

Synthesis of Alloc-pAph-Glu-Gly-Cha-NH_2

[0076] To 0.150g of Rink resin (substitution 0.78mmol/g), after Fmoc-deprotection, the following protected amino acids were coupled according to general procedure, described in Example 1: Fmoc-Cha-OH, Fmoc-Gly-OH, Fmoc-Glu(OtBu)-OH and Alloc-pAph-OH. The peptide was cleaved and deprotected by mixture TFA/thioanisole (95/5) for 1 hour and processed as described in Example 1. The crude compound was purified using HPLC as described in Example 1 and characterized by MS. (M+H)+: found 630.1, calc. 630.3.

Example 15

Synthesis of Alloc-pAph-Glu-Asn-(-CH_2-CH_2-Ph)Gly-NH_2

[0077] For N-substituted glycines, the procedure of Zuckermann et al. (J. Am. Chem. Soc. 114:10646(1992), which is incorporated herein by reference) was used.

[0078] To 0.1g of Rink resin (substitution 0.78mmol/g), after Fmoc-deprotection, bromoacetic acid was coupled via symmetrical anhydride in DCM/DMF. After 10 minutes, the resin was washed with DCM and the coupling repeated once more. After washing with DCM and DMF, the resin was treated with 1M solution of phenethyl amine in DMSO overnight. After DMF washing, the resin was reacted with symmetrical anhydride of Fmoc-Asn(Trt)-OH in DCM/DMF. After Fmoc-deprotection, according to general procedures in Example 1, following protected amino acids were coupled: Fmoc-Glu(OtBu)-OH and Alloc-pAph-OH. The peptide was cleaved and deprotected by mixture TFA/thioanisole (95/5) for 1 hour and processed as described in Example 1. The crude compound was purified using HPLC as described in Example 1 and characterized by MS. (M+H)+: found 694.9, calc. 695.3

Example 16

Synthesis of Alloc-pAph-Glu-Thr(Bzl)-NH-CH_2-CH_2-$CH(Ph)_2$

H-Thr(Bzl)-NH-CH_2-CH_2-$CH(Ph)_2$ · HCl

[0079] 0.62g (2 mmol) of Boc-Thr(Bzl)-OH were dissolved in 10 ml DCM, 2 mmol of triethylamine were added and the solution was cooled to 0°C. With stirring, 2 mmol of isobutylchloroformate were slowly added. With cooling bath

Example 20

Synthesis of Alloc-pAph-Glu-Asn-NH-CH_2-CH_2-Ph

2-(S)-[2-(S)-Allyloxycarbonylamino-3-(4-carbamimidoyl-phenyl)-propionylamino]-pentanedioic acid 5-tert-butyl ester 1-methyl ester; hydrochloride

[0084] To 2-(S)-allyloxycarbonylamino-3-(4-carbamimidoyl-phenyl)-propionic acid; hydrochloride (3.48 g, 10.6 mmol) and 2-(S)-amino-pentanedioic acid 5-tert-butyl ester 1-methyl ester; hydrochloride (2.7 g, 10.6 mmol) in 20 ml of DMF were added at -15°C TOTU (3.83 g, 11.67 mmol) and N-ethylmorpholine (2.7 ml, 21.2 mmol). The mixture was stirred for 1 hour and then allowed to warm to room temperature. After evaporation ethyl acetate was added to the residue and the organic layer was extracted with aqueous sodium hydrogen carbonate solution, potassium hydrogen sulfate solution and water. The organic layer was evaporated. Yield: 2.8 g; (50%), MS 491.3 (M + H)+.

2-(S)-[2-(S)-Allyloxycarbonylamino-3-(4-carbamimidoyl-phenyl)-propionylamino]-pentanedioic acid 5-tert-butyl ester

[0085] To 2-(S)-[2-(S)-Allyloxycarbonylamino-3-(4-carbamimidoyl-phenyl)-propionylamino]-pentanedioic acid 5-tert-butyl ester 1-methyl ester; hydrochloride (3.06 g, 5.8 mmol) in 100 ml of water and 30 ml of THF was added lithium hydroxide hydrate (0.49 g, 11.6 mmol). The solution was stirred at room temperature for 12 hours, evaporated and freeze-dried. The residue was purified by chromatography on Sephadex LH20 employing n-butanol (17): glacial acetic acid (1): water (2) as eluent. Pure fractions were combined. The solvent was evaporated, the residue was taken up in water and the aqueous solution was freeze-dried. Yield: 2.7 g; (97%), MS 477.4 (M + H)+.

4-(S)-[2-(S)-Allyloxycarbonylamino-3-(4-carbamimidoyl-phenyl)-propionylamino]-4-(2-carbamoyl-1-(S)-(2-phenylethyl-carbamoyl)-ethylcarbamoyl)-butyric acid; hydrochloride
(Alloc-pAph-Glu-Asn-NH-CH_2-CH_2-Ph)

[0086] To 2-(S)-[2-(S)-Allyloxycarbonylamino-3-(4-carbamimidoyl-phenyl)-propionylamino]-pentanedioic acid 5-tert-butyl ester (48 mg, 0.1 mmol) and 2-(S)-Amino-N1-phenethyl-succinamide; hydrochloride (27 mg, 0.1 mmol) in 5 ml of DMF were added at 0°C HATU (39 mg, 0.1 mmol) and collidine (24.2 mg, 0.2 mmol). The mixture was stirred for 1 hour and then allowed to warm to room temperature. After evaporation the residue was purified by chromatography on Sephadex LH20 employing n-butanol (17): glacial acetic acid (1): water (2) as eluent. Pure fractions were combined. The solvent was evaporated, the residue was taken up in water and the aequous solution was freeze-dried. Yield: 45 mg; (66%), MS 638.4 (M + H)+.

Example 21

Synthesis of Alloc-pAph-Glu-Asn-NH-(3-chlorobenzyl)

[0087] To 2-(S)-[2-(S)-Allyloxycarbonylamino-3-(4-carbamimidoyl-phenyl)-propionylamino]-pentanedicic acid 5- tert-butyl ester (50 mg, 0.105 mmol) and 2-(S)-Amino-N1-(3-chlorobenzyl)-succinamide; trifluoroacetate (61mg, 0.16 mmol) in 5 ml of DMF were added at 0°C TOTU (36 mg, 0.11 mmol) and N-ethylmorpholine (57 µl, 0.4 mmol). The mixture was stirred for 1 hour and then allowed to warm to room temperature. After evaporation the residue was purified by chromatography on Sephadex LH20 employing n-butanol (17): glacial acetic acid (1): water (2) as eluent. Pure fractions were combined. The solvent was evaporated, the residue was taken up in water and the aequous solution was freeze-dried. Yield of 4-(S)-[2-(S)-allyloxycarbonylamino-3-(4-carbamimidoyl-phenyl)-propionylamino]-4-(2-carbamoyl-1-(S)-(3-chlorobenzylcarbamoyl)-ethylcarbamoyl)-butyric acid (Alloc-pAph-Glu-Asn-NH-(3-chlorobenzyl): 28 mg; (41%), MS m/z 658.3 $(M + H)^+$.

Example 22

Determination of Ki for FVIIa inhibitor

[0088] The inhibitory activity (Ki) of each compound towards factor VIIa/tissue factor activity was determined using a chromogenic assay esentially as described previously (Ostrem J A, Al-Obeidi F, Safar P, Safarova A, Stringer S K, Patek M, Cross M T, Spoonamore J, LoCascio J C, Kasireddy P, Thorpe D S, Sepetov N, Lebi M, Wildgoose P, Strop P, Discovery of a novel, potent, and specific family of factor Xa inhibitors via combinatorial chemistry. Biochemistry 1998,37,1053-1059). Kinetic assays were conducted at 25 °C in half-area microtiter plates (Costar Corp., Cambridge,

B3 is C(O),

D is the group D1-D2-D3, wherein

D1 is NR80, wherein R80 is selected from the group consisting of hydrogen, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl and heterocycloalkylalkyl,

D2 is CR81R82, wherein R81 and R82 are independently selected from the group consisting of hydrogen and unsubstituted or substituted alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl and heterocycloalkylalkyl,

D3 is C(O),

E_n is $(E1\text{-}E2\text{-}E3)_n$, wherein

n is an integer of from 0 to 3,

E1 is NR70, wherein R70 is selected from the group consisting of hydrogen, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl and heterocycloalkylalkyl,

E2 is CR71R72, wherein R71 and R72 are independently selected from the group consisting of hydrogen and unsubstituted or substituted alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl and heterocycloalkylalkyl,

E3 is C(O),

R2 is selected from the group consisting of NR21R22, OR23 and R24, wherein R21, R22, R23 and R24 are independently selected from the group consisting of hydrogen and unsubstituted or substituted alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl and heterocycloalkylalkyl,

and pharmaceutically acceptable salts thereof.

2. The compound of claim 1, wherein the radicals of R12 can be substituted with a substituent selected from the group consisting of halogen, CF_3, hydroxy, nitro, amino, cyano, carboxy, aminocarbonyl, alkylsulfonyl, aminosulfonyl, alkoxy, alkylcarbonylamino and mono- or di-alkylamino.

3. The compound of claim 1, wherein R92 and R93 independently are selected from the group consisting of alkyl, phenyl, phenylalkyl and pyridylalkyl, which can be substituted with a substituent selected from the group consisting of alkyl, alkoxy, alkylamino, dialkylamino, tetraalkylammonium, aminoalkylaryl, aminoarylalkyl, hydroxycarbonyl, halogen, hydroxy, amino, aminocarbonyl, amidoxime, acylimido, amidino, guanidino, alkoxycarbonylamino, alkoxycarbonylamidino, alkoxycarbonylguanidino, triazolyl and alkylsulfonyl.

4. The compound of claim 1, wherein the radicals of R96 and R97 can be substituted with a substituent selected from the group consisting of hydroxycarbonyl, aminocarbonyl, alkylated aminocarbonyl, alkoxycarbonyl, tetrazol, hydroxysulfonyl, aminosulfonyl and phosphonic acid.

5. The compound of claim 1, wherein the radicals of R81 and R82 can independently be substituted with a substituent selected from the group consisting of amino, aminocarbonyl, amidino, guanido, aminoalkyl, hydroxy, mercapto, which can be substituted with a protecting group, and acetimido, nitro and cyano.

6. The compound of claim 1, wherein the radicals of R71 and R72 can independently be substituted with a substituent selected from the group consisting of alkyl, alkoxy, halogen, CF_3, nitro, cyano, alkylsulfonyl and alkylcarbonyl.

7. The compound of claim 1, wherein the radicals of R21, R22, R23 and R24 can independently be substituted with halogen, CF_3, hydrogen, nitro, cyano, alkoxy, alkylsulfonyl, aminosulfonyl and =O.

8. The compound of claim 1, wherein the mentioned linear or branched alkyl chains have 1 to 6 carbon atoms, the unsaturated linear or branched alkenyl and alkynyl chains have 2 to 6 carbon atoms, the cyclic alkyl groups have 3

B is selected from the group consisting of glutamic acid, glutamic acid ester and a pharmaceutically acceptable salt of glutamic acid,

D is a residue selected from the group consisting of Arg, Dap, Dab, Orn, Lys, Dap[-C(=NH)-NH_2], Dab[-C(=NH)-NH_2], Lys[-C(=NH)-NH_2], Asn, Ser, Thr, Ser(Bzl), Arg(NO_2), Trp, Phg, Ala, Val, Ile, Leu, Phe, 2-Abu, Ala(3-CN), Ala(3-amidino), 2-Abu(4-CN), 2-Abu(4-amidino),

E is a residue selected from the group consisting of Cha, Chg and Phe[4-C(-S-CH_2-CH_2-S-)-Ph],

R22 is hydrogen or a radical selected from the group consisting of benzyl, phenethyl, 3-phenylpropyl, fluorenyl, diphenylmethyl, diphenylethyl and diphenylpropyl, which radicals may be substituted with a substituent selected from the group consisting of F, Cl, Br, hydroxy, methoxy, nitro, cyano, alkylsulfonyl, aminosulfonyl and trifluoromethyl.

18. The compound of claim 10, which is

Alloc-pAph-Glu-Arg-Cha-NH_2,
Allylaminocarbonyl-pAph-Glu-Arg-Cha-NH_2,
Alloc-pAph-Glu-Arg-Chg-NH_2,
Alloc-pAph-Glu-Dap[-C(=NH)-NH_2]-Cha-NH_2,
Alloc-pAph-Glu-Ala[3-C(=NH)-NH_2]-Cha-NH_2,
Alloc-pAph-Glu-Asn-Cha-NH_2,
Alloc-pAph-Glu-Dab-Cha-NH_2,
Alloc-pAph-Glu-Dap[-C(=NH)-NH_2]-NH_2,
Alloc-pAph-Glu-Gly-Cha-NH_2,
Alloc-pAph-Glu-Thr(Bzl)-NH-$(CH_2)_2$-CH$(Ph)_2$,
Alloc-pAph-Glu-Dab-NH-CH_2-CH_2-phenyl,
Alloc-pAph-Glu-Asn-NH-CH_2-Chx,
Alloc-pAph-Glu-2-Abu[4-C(=NH)-CH_3]-Cha-NH_2,
Alloc-pAph-Glu-Dap[-C(=NH)-CH_3]-Cha-NH_2,
Alloc-pAph-Glu-Dab[-C(=NH)-NH_2]-Cha-NH_2,
Alloc-pAph-Glu-2-Abu[4-CN]-Cha-NH_2,
Alloc-pAph-Glu-Ala[3-CN]-Cha-NH_2,
Alloc-pAph-Glu-Asn-(1-naphthyl)-methylamide,
Alloc-pAph-Glu-Asn-(1-naphthyl)-1-ethylamide,
Alloc-pAph-Glu-Asn-(2-naphthyl)-methylamide,
Alloc-pAph-Glu-Asn-(3,4-dichlorobenzyl)-amide,
Alloc-pAph-Glu-Asn-2-(3-chlorophenyl)-ethylamide,
Alloc-pAph-Glu-Arg[NO_2]-Cha-NH_2,
Alloc-pAph-Glu-Cys[Bzl]-Cha-NH_2,
Alloc-pAph-Glu-Trp-Cha-NH_2,
Alloc-pAph-Glu-Phg-Cha-NH_2,
Alloc-pAph-Glu-Asn-(9-fluorenyl)-amide, or
Alloc-pAph-Glu-Asn-(3,5-ditrifluormethylbenzyl)-amide,

and pharmaceutically acceptable salts, amides, esters thereof.

19. A process for the preparation of a compound as defined in claim 1, which comprises

a1) attaching a compound of the formula Fmoc-E_n-OH or Fmoc-D1-D2-COOH, where Fmoc is 9-fluorenylmethoxycarbonyl and E_n, D1 and D2 are defined as in claim 1, to an acid sensitive linker coupled to a solid support, and cleaving off the protecting group Fmoc,
a2) repeating the procedure as described in step a1) above with Fmoc-B1-B2-COOH,
a3) repeating the procedure as described in step a1) above with R1-A1-A2-COOH, and
a4) finally cleaving off the compound obtained according to steps a1) through a3) above by means of TFA from the resin, where TFA is trifluoroacetic acid,
or
b1) coupling the side chain carboxylic acid of Fmoc-B1-CH(R97)-COOPG, where Fmoc is as defined in step a1) above, R97 is a radical as defined in claim 1 except hydrogen, which is substituted with a hydroxycarbonyl group, and PG is a protecting group, to an acid sensitive benzylalcohol type of linker attached to an amino functionalized resin,

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which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 98 11 7506

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	WO 89 09612 A (CORVAS INC) 19 October 1989 * the whole document *	1-5,7,8,19-22	C07K5/11 C07K5/09 A61K38/06 A61K38/07
X	WO 90 03390 A (CORVAS INC) 5 April 1990 * claims 1,2,6-8,10,17-19; tables I-III *	1-10,14,16,19-22	
X	WO 91 07432 A (UNIV TEXAS) 30 May 1991 * claims 1-3,6,8,9,27,30,31,34-37; tables I-IV *	1-10,14,16,19-22	
X	WO 95 00541 A (HOLMES MICHAEL JOHN ;HAFSLUND NYCOMED AS (NO); STEPHENS ROSS WENTW) 5 January 1995 * the whole document *	1-10,14,16,19-22	
X	WO 96 40779 A (MATTHEWS DEREK PETER ;NYCOMED IMAGING AS (NO); OERNING LARS (NO);) 19 December 1996 * claims 14,6-12; examples 4,5; table I *	1-10,14,16,19-22	
	-/--		

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

C07K
A61K

INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
THE HAGUE	5 March 1999	Groenendijk, M

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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INCOMPLETE SEARCH SHEET C

Application Number
EP 98 11 7506

Although claim 21 IS directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

Claim(s) searched completely:
17,18

Claim(s) searched incompletely:
1-16,19-22

Reason for the limitation of the search:

The scope of the claims 1-16 is very broad and speculative. A formula consisting virtually of variables which are moreover in at least part of the claims ill-defined (e.g. the use of "alkyl", "aryl" and "heteroaryl") cannot be considered to be a clear and concise definition of patentable subject-matter (Art.84 EPC).
Furthermore the available experimental data actually only comprise a very small part of the compounds claimed, which part is moreover not evenly distributed over the whole claimed area. Therefore the claims can also not be considered to represent a permissible generalisation which is fairly based on experimental evidence, that is, they are also not adequately supported by the description (Art.84 EPC).
Therefore a meaningful and economically feasible search could not encompass the complete subject-matter of the claims. Consequently the search had been limited to the actually synthesised examples and (closely) related analogs, that is the compounds encompassed by the claims 17 and 18 (see also the examples 3-21) and also the claims 19-22 as far as relating to said compounds, and has been extended to compounds having the same activity(Rule 45 EPC, Guidelines BIV,2.1 and BVIII, 5 and 6).

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 98 11 7506

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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05-03-1999

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5663297 A		JP 2264795 A	29-10-1990
		JP 6062672 B	17-08-1994
		MX 19467 A	01-11-1993
		PT 93245 A,B	31-08-1990
		RU 2024549 C	15-12-1994
WO 9529189 A	02-11-1995	AU 2368395 A	16-11-1995
		CA 2186497 A	02-11-1995
		CN 1147261 A	09-04-1997
		CZ 9603140 A	14-05-1997
		EP 0758341 A	19-02-1997
		FI 964317 A	25-10-1996
		HU 76346 A	28-08-1997
		JP 10503477 T	31-03-1998
		LT 96151 A,B	26-05-1997
		LV 11740 A	20-04-1997
		LV 11740 B	20-12-1997
		NO 964553 A	27-12-1996
		NZ 284977 A	24-09-1998
		PL 317067 A	03-03-1997
		SI 9520044 A	31-10-1997
		SK 136696 A	07-05-1997
		US 5849510 A	15-12-1998
		ZA 9503361 A	12-01-1996

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